

REMARKS

Claims 2, 4-6, 17-20 and 22-70 have been canceled.

Claims 1, 3 and 16 have been amended.

Claims 1 and 16 have been amended to recite “a method of treating nausea, vomiting, retching or any combination thereof in a subject in need thereof, wherein the nausea, vomiting, retching or any combination thereof is caused by an anesthetic, radiation, a cancer chemotherapeutic agent, a toxic agent, an odor, a medicine, pregnancy, motion, a condition which is associated with vertigo, headache or a malady of the gastrointestinal (GI) tract....” Support for these amendments is found in the specification, for example at page 7, line 16 to page 8, line 18 and page 32, line 17 to page 33, line 5.

Claim 3 has been amended to depend from Claim 1 in view of the cancellation of Claim 2.

No new matter has been added. Therefore, entry of the amendments into the application is respectfully requested.

Rejection of Claims 1, 7-16 and 21 Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 1, 7-16 and 21 under 35 U.S.C. § 112, first paragraph as lacking enablement because the specification “does not reasonably provide enablement for the treatment of nausea, vomiting etc. from all sources....”

Applicants respectfully disagree. The claims are enabled if the person of skill in the art could make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *Id.* at 737, 8 USPQ2d at 1404.

In an effort to expedite prosecution, Applicants have incorporated the subject matter of non-rejected Claims 2 and 4-6 into independent Claim 1 and non-rejected Claims 17-20 into independent Claim 16. As such, the rejection of independent Claims 1 and 16 is moot. The rejection of the remaining claims is also moot in view of the dependence of same on either independent Claim 1 or independent Claim 16.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-21 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-21 under 35 U.S.C. § 103(a) as being unpatentable over Wu *et al.*, “Effects of Acute and Chronic Administration of MCI-225, a New Selective Noradrenaline Reuptake Inhibitor with 5-HT₃ Receptor Blocking Action, on Extracellular Noradrenaline Levels in the Hypothalamus of Stressed Rats,” *Jpn. J. Pharmacol.* 83:31-38 (2000) (hereinafter “Wu”) in view of Turconi *et al.* (U.S. Patent No. 5,223,511) (hereinafter “Turconi”). The Examiner stated that Wu teaches that MCI-225 is a 5-HT₃ receptor antagonist, and that Turconi teaches the use of 5-HT receptor antagonists to treat emesis. The Examiner concluded that one of ordinary skill in the art would be motivated to combine Wu and Turconi to arrive at the claimed invention.

Applicants respectfully disagree. Wu teaches that MCI-225 is a compound having a mixed pharmacology which exhibits both selective inhibition of noradrenaline (NA) reuptake and blocking action of the 5-HT₃-receptor. Wu’s report, however, is limited to the effect of MCI-225 on extracellular NA levels and provides no data relating to the 5-HT₃ receptor blocking action. Wu concludes from the studies on NA reuptake that detailed mechanisms for the pharmacological actions of MCI-225 are unclear, that changes in monoamine metabolism and/or NA transport might be involved and that the data suggest the possibility that MCI-225 might possess anxiolytic and/or antidepressant properties.

Additional details relating to the pharmacological profile of MCI-225 are provided in Eguchi *et al.*, “Pharmacological Profile of the Novel Antidepressant 4-(2-Fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno-[2,3-d]pyrimidine Monohydrate Hydrochloride,” *Arzneimittel-Forschung* 47: 1337-1347 (1997) (hereinafter “Eguchi”) (Exhibit A), which is cited as reference number 4 in Wu. Eguchi discloses that MCI-225 is a selective NA reuptake inhibitor with 5-HT₃ receptor antagonist action (Page 1346) and serotonin reuptake inhibition (Table 2). Based on the combined teachings of Wu and Eguchi, one of ordinary skill in the art would not select MCI-225, as a substitute for the 5-HT receptor blocking agents of Turconi, with any reasonable expectation of success, because:

- (1) drugs with NA reuptake activity are known to cause (not treat) emesis, and MCI-225 is a NA reuptake inhibitor;

- (2) the mechanisms for the pharmacological actions of MCI-225 are unclear and complex in comparison to drugs that are primarily 5-HT receptor antagonists;
- (3) Wu reports data of NA reuptake activity, but provides no data on 5-HT receptor blocking action; and
- (4) MCI-225 is pharmacologically distinct from the typical 5-HT₃ receptor antagonist ondansetron (Zofran).

Each of these points are discussed in detail below.

First, the art teaches that nausea is a side effect of the administration of NA reuptake inhibitors. For example, atomoxetine and reboxetine, both of which are selective NA reuptake inhibitors, are taught to have nausea as a side effect when used for the treatment of depression. Because MCI-225 is a selective NA reuptake inhibitor, one of ordinary skill in the art would not be motivated to substitute a drug which possesses an activity known to cause nausea, to treat nausea, with any reasonable expectation of success. See the following in support of nausea as a side effect of NA reuptake inhibitors: Montgomery, "Predicting Response: Noradrenaline Reuptake Inhibition," *Int. Clin. Pharmacol.* 14(1):S21-6 (1999). (Exhibit B); Scates *et al.*, "Reboxetine: A Selective Norepinephrine Reuptake Inhibitor for the Treatment of Depression," *Ann. Pharmacother.* 34:1302-12 at page 1307 (Exhibit C) and STRATTERATM Package Insert at page 13, last paragraph and page 14, Tables 2 and 3 (Exhibit D).

Second, Wu does not teach or suggest that MCI-225, a compound with mixed pharmacology, can be substituted for a drug being relied on specifically for its 5-HT receptor blocking action. In contrast, Wu concludes that detailed mechanisms for the pharmacological action of MCI-225 are unclear. Such a lack of certainty in the behavior of MCI-225 would not motivate one of ordinary skill in the art to use MCI-225 as a substitute for a drug being relied on for its 5-HT receptor blocking activity, with any reasonable expectation of success.

Third, Wu, in fact, does not report on the 5-HT receptor blocking action of MCI-225, but rather reports on the selective NA reuptake inhibition. One of ordinary skill in the art would not be motivated to use MCI-225 for its 5-HT receptor blocking activity based on a report directed solely to MCI-225's NA reuptake inhibitor activity.

Fourth, even though Eguchi provides additional details on the serotonin blocking action of MCI-225, the results reported therein suggest that MCI-225 does not behave as the typical selective 5-HT₃ receptor antagonist, ondansetron (Zofran), mentioned by the Examiner. For example, Eguchi reported that MCI-225 inhibited the von Bezold-Jarisch reflex in rats with an ID₅₀ of 22.2 mg/kg, indicating 5-HT₃ receptor antagonist action. In the same study, the ID₅₀ for the 5-HT₃ receptor antagonist ondansetron (Zofran) was 0.29 mg/kg, which is almost 100 times more potent than MCI-225. See Exhibit A at page 1344, paragraph 3.13. As such, one of ordinary skill in the art would not substitute MCI-225 for a selective 5-HT₃ receptor antagonist such as Zofran, with any reasonable expectation of achieving a successful treatment due MCI-225's significantly reduced 5-HT₃ receptor antagonist activity and its additional and potent NA reuptake inhibitor activity.

Provisional Rejection of Claims 1-21 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner has provisionally rejected Claims 1-21 under the judicially created doctrine of obviousness-type double patenting over Claims 71-158 of copending U.S. Serial No. 10/846,978 and Claims 71-158 of copending U.S. Serial No. 10/846,979.

Applicants note this rejection and, to expedite prosecution, will file a terminal disclaimer upon indication that the only remaining rejections are the Double Patenting rejections.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By

Christine M. Wise

Christine M. Wise

Registration No. 58,073

Telephone: (978) 341-0036

Facsimile: (978) 341-0136

Concord, MA 01742-9133

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